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Dated 18 July 2000

GB9915686.1

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ASTRAZENECA UK LIMITED
Incorporated in the United Kingdom
15 Stanhope Gate
LONDON
W1Y 6LN
United Kingdom

[ADP No. 07810294001]

Patents Form 1/77

Patents Act 1977
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1. Your reference — PHM 99-052

2. Patent application number *(The Patent Office will fill in this part)* — 9915686.1 — 06 JUL 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Zeneca Limited
15 Stanhope Gate
LONDON W1Y 6LN
Great Britain

SECTION 30 (1977 ACT) APPLICATION FILED 9/3/00

Patents ADP number *(if you know it)*

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — DEVICE

5. Name of your agent *(if you have one)*

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Global Intellectual Property
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
Great Britain

Patents ADP number *(if you know it)*

1030618002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Lynda M Slack Date 5 July 1999

Zeneca Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Lynda M Slack 01625 516173

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DEVICE

The invention relates to a micro-fabricated device for the measurement of the solubility or the rate of dissolution of a sample. Specifically the invention relates to an automated device for the determination of these parameters on large numbers of samples.

The determination of the solubility of a sample or its rate of dissolution are important in various areas of the drug discovery process since many processes of interest to the research scientist are dependant on the solubility or rate of dissolution of the sample. Examples where this information is of value would include interpreting data of a sample in an *in vitro* assay, oral absorption test, formulation studies, and *in vivo* bioavailability studies.

Currently the pace of change in techniques and tools for discovery of biologically active molecules is increasing with the ability of combinatorial chemistry and multi parallel synthesis (MPS) to rapidly provide large numbers of diverse samples to enter into the drug discovery process. In addition the mapping and sequencing of the genomes of many plants, animals and parasites, and the human genome, is already providing a growing number of new targets which may be used in biological tests. In the future it is to be expected that the number of biological targets is to grow even further. It is estimated that in the last 100 years of research only 400 human drug targets have been discovered whilst the human genome project will have sequenced at least 100,000 genes, many of which will code for important biological targets for drug therapy.

However, synthetic techniques such as multiple parallel synthesis (MPS) and combinatorial chemistry provide relatively small sample sizes, for example in the microgram range. The limited sample sizes currently produced are not large enough to supply more than a few tests within the drug discovery process before the supply is exhausted. Therefore, resynthesis is required in order to restock the chemical library.

In order to accelerate the rate of discovery of biologically active molecules, there is currently considerable interest in the measurement of physicochemical properties very early in the discovery process so that these factors may be used to influence future decisions on which molecules to synthesis as samples for future testing. However, as described above, samples of potential interest may only be available in relatively small amounts i.e. <1 mg. There is therefore a strong need for methods of measuring solubility and rate of dissolution that can be

applied to large numbers of samples without requiring proportionately more resources, and which are capable of dealing with small sample sizes. Conventional methods often employ complex separation steps which are time-consuming. Although these can be automated, the serial nature of the analysis, i.e. one sample at a time, still effectively limits the throughput. Automation may also lead to increased compound demands which is counter to the thrust of modern synthetic methods such as combinatorial chemistry and MPS and related technologies which, typically, do not produce large quantities of material. Therefore, for the large number of samples which are being prepared for testing, the traditional methods of measuring physicochemical properties are now prohibitively expensive and time consuming and can be performed on no more than a small percentage of the samples being prepared.

Currently the techniques for the determination of solubility involve stirring the sample in an appropriate solvent till a saturated solution has been achieved removing the excess compound, typically by filtration or centrifugation, and then analysing the resulting solution using some physical method, for example HPLC, MS or UV detection, one example of which is direct UV analysis. This method is tedious, labour intensive, requires a sample size of at least 1mg, and the requirement for a physical separation can result in the production of erroneous data. One disadvantage of this technique is that fine solid particles may be suspended in the saturated solution. To avoid this disadvantage separation techniques need to be thorough, for instance centrifugation typically is required at least twice for each sample, which adds further to the expense and time needed to achieve a measurement. To determine the rate of dissolution of a sample involves the need to make a number of measurements over a period of time. This increases test times, and also proportionately the amount of sample required.

Therefore, there is a need to find simple, sensitive, high throughput approaches to the measurement of the solubility or rate of dissolution of a sample, especially in the pharmaceutical and agrochemical industry. Such a system should use small sample sizes, be quick (less than 3 hours) and be amenable to operation by a machine with minimal operator input. In particular, miniaturised approaches operating on the picolitre / nanolitre / microlitre scale are particularly desirable, because of the large cost savings, potential for high throughput, and use of small sample sizes. Currently we are aware of no such techniques available which fulfil all the above requirements.

Micro-fabricated devices have been used to develop laboratory techniques on the micro scale which require minimal operator involvement using very small amounts of sample.

Micro-fabrication techniques are generally known in the art using tools developed by the semiconductor industry to miniaturise electronics, it is possible to fabricate intricate fluid systems with channel sizes as small as a micron. These devices can be mass-produced inexpensively and are expected to soon be in widespread use, for example, in simple analytical tests. See, e.g., Ramsey J.M. et al. (1995), "Micro-fabricated chemical measurement Systems," Nature Medicine 1:1093-1096; and Harrison, D.J. et al (1993), "Micro-machining a miniaturized capillary electrophoresis-based chemical analysis system on a chip," Science 261:895-897.

Miniaturisation of laboratory techniques is not a simple matter of reducing their size. At small scales different effects become important, rendering some processes inefficient and others useless. It is difficult to replicate smaller versions of some devices because of material or process limitations. For these reasons it is necessary to develop new methods for performing common laboratory tasks on the micro-scale.

Devices made by micro-machining planar substrates have been made and used for chemical separation, analysis, and sensing. See, e.g., Manz, A. et al. (1994), "Electroosmotic pumping and electrophoretic separations for miniaturized chemical analysis system," J. Micromech. Microeng. 4:257-265.

We have devised a micro-fabricated device which can be used to determine solubility and rate of dissolution with minimal operator involvement using very small amounts of sample.

We disclose as the first feature of the invention a micro-fabricated solubility measuring system comprising a microfabricated device having a region in the device for receiving solid sample and a liquid inlet for introducing a predetermined amount of a liquid to the region together with a detector which determines directly or indirectly the amount of solid sample removed from the region by the liquid.

In this disclosure, the term "sample" includes any material, single compound or mixture, which may be put into solid form, whether biological or chemical, preferably the sample is an organic synthetic compound, ideally of MW <1000.

In this disclosure, the term "region" means an area within the micro-fabricated device, which is able to accept and retain an amount of solid sample and allow that solid sample to come into contact with liquid in the device. The region may be formed as a surface on which solid material can be deposited and adhere as a continuous or discontinuous layer. Such a surface may already be part of the surface of the micro-fabricated device or may be applied as a coating. Preferably the surface incorporates one or more physical structures, such as indents, which aid retention of defined quantities of solid sample. The volume defined by the indent may be in the range of sizes which may be created in micro-fabricated devices as described above, such as by etching or building up structures or by moulded replication of structures. The indents may be sufficiently large to retain all the sample or large enough to retain at least part of the sample the remaining part being above the indent. Typical indent volumes include from 1 nl to 1 µl. Typical dimensions across indents may be in the range of sizes which may be created in micro-fabricated devices, typical ranges are from 10-1000µm, preferably 10-100µm. Indents may be in the form of extended slots or grooves where the long dimension may exceed 1000µm. It will be appreciated that any number of indents may be arranged on the same device, such as to form a pattern, such as a line or grid pattern. An indent may be formed by a depression in the surface of the microfabrocate device or within a raised structure on the microfabricated device.

The process of deposition of sample into the region may involve compaction such that the solid cannot be physically washed away but must be removed by a process of dissolution, see Fig 1. Alternatively the sample may be deposited by other processes of application such as a spray or, alternatively, the sample may be deposited from a solution by creating local environments in the region, such as a hydrophobic surface, which forces the compound out of solution, or by evaporation of the liquid and subsequent deposition of the sample. The process of deposition may be assisted by use of coatings to the surface of the region to attract and bind the sample. The solid sample is transferred to the region so that the amount and thickness of sample is controlled and measurable. Control of sample amount and thickness may be facilitated by features such as indents in the surface of the sample receiving region or by other means such as by applying sample to the microfabricated surface through a screen of known thickness, by controlling weight or volume of sample, and by deposition to the

microfabricated surface of more sample than required and then removing excess by machining or etching means, and by combinations of such procedures. Sample deposition methods may include pressing solid sample onto a receiving surface, or deposition of mixtures or solutions of the sample in volatile carrier fluid. Samples may not be pure. Additionally the sample may contain solid material which may be insoluble in the solvent used to determine the solubility measurement and added to the sample to aid deposition and/or for formation of a controlled thickness of sample. Such solid materials which may be added may include fibres or ballotini.

The term "detector" includes devices, probes, sensors or such like which are able to determine the presence or absence of solid sample remaining in the region, either with or without the liquid present, or which are able to measure the amount of solid sample remaining or removed from the region. The detector may operate alternatively by measuring sample present in the liquid. Examples of such detector methods include interferometry where the intensity of interference patterns of reflected light on the surface of the device show the depth of sample in indents, surface acoustic wave sensors, elipsometry, use of radiation sources and sensors measuring attenuation though the solid sample layer, image analysis, spectrophotometry, chromatography or electrophoresis. The detector of the system may be separate to the micro-fabricated aspects of the system ("off-device") or in a preferred option may also be an integrated micro-fabricated feature of a micro-fabricated solubility device ("on-device"). A variety of different detection methods are described below as preferred features:

1. The thickness of the solid sample is defined by means of a micro-engineered feature such as an indent which allows integral calibration for detection methods applied to a range of solid samples whose physical properties such as refractive index and spectral absorbencies are not known a priori. This is particularly valuable for elipsometry.

2. Most solid samples of interest are insulators or at least poor conductors of electricity. Dissolution of such solid samples from an electrode surface into an ionically conducting liquid may be monitored by electrical impedance measurements. Indents formed so that the base only of indents is electrically conducting allows those

conductiv bases to be used as electrodes. Coverage of the conductive indent bases may be mo itored using electrical impedance between electrode and solution, with a substantial ecrease in impedance signalling the dissolution of material covering the elect ode.

3. Direct detection or mc asuremen of the disso ved sample in solution can be difficult, such as by the use of UV detec ion, if the s mple is only weakly absorbing or fluore cent. An alternative indirect technique may b used which utilises direct measuring tech iques which employs the use of an indicator material . A thin layer of a selected indicator material deposited on the solid rece ving region is then covered with the solid sample. Preferably th indicator material s deposited as a thin film over the bases of any indent which is the n filled with solid sam le. Release of the indicator material into solution is delayed un l sample dissolution i near completion, and its appearance if solution acts as an end point signal. Indicat r materials may be detected on or off device by the use of, for ex mple, UV detection f fluorescent compounds. Low mobility a d relatively low solu ility, in the solvent sed, indicator compounds are preferred so that the indicator does not permeate throu h the sample nor promote release of the sample from the surfac .

4. As an alternative to producing indent type structures in the solid sample receiving region which are filled with sample and then progressively revealed as dissolution proceeds an optically monitorable feature may be produced by a series of features made from solid sample on a plane surface of the microfabricated device. These features may form diffraction structures. Where the diffraction structures are formed by indents the process of sample dissolution allows development of the diffraction pattern, while for diffraction structures formed from the sample on a plane surface the process of dissolution is accompanied by a decrease in the size of the features and reduction in the intensity of any diffraction effects. Such raised features formed from the solid samples may be formed by deposition through masks or grids but do require that the sample adheres well to the substrate surface. The use of

indented structures provides more tolerance of variation in physical properties and sample substrate adhesion.

Additionally the device may contain an outlet for removal of the liquid where the liquid is desired to be removed in order for the particular detector used to make the requisite measurement.

We disclose as a further feature of the invention a method for determining the solubility of a sample in a micro-fabricated device the method comprising:

(1) introducing a predetermined amount of liquid to a solid sample containing region within the micro-fabricated device;

(2) measuring the amount of solid sample removed from the region by the liquid;

(3) determining the solubility of the sample by reference to the measurement of solid sample removed from the region and the amount of liquid used.

Due to the smaller quantities of liquid and sample which may be used diffusional distances within the liquid can be dramatically lowered allowing for equilibrium to be reached efficiently without the need for convective or advective mixing. However movement of liquid may be employed to enhance or control dissolution rates.

Different samples will reach the point of equilibrium at different rates, this is known as the rate of dissolution. The rate of dissolution of a sample may be affected by many different factors such as the morphology or surface area of the sample, chemical kinetic factors at the solid/ solution interface, permeation of pores within the solid by solvent, and transport of dissolved material in the solvent by convective, advective, or diffusive processes. Within microstructures it is possible to limit convective or advective and in particular turbulent fluid transport so that diffusion may be the dominant mode of transport of dissolved material. Where diffusive transfer is the limiting factor the dissolution rate is related to the length of the path through which the dissolved solute molecules diffuse and the geometry of the fluid body. Diffusive transfer rates will generally be inversely related to the square of the path length.

Typically diffusion coefficients (D) of samples of the size range of interest (MW of a few hundred) will be $\sim 10^{-6}$ cm^2s^{-1} and have diffusive transfer times across a path length (L) which may be derived from expressions of the type $Dt/L^2 = 0.01$ to 1 second, where Dt/L^2 =

0.01 approximates to a diffusion front reaching a distance L from source plane, and $Dt/L^2 = 1$ corresponds to near completion of the diffusive process (concentration gradient across L being nearly eliminated). Approximate times for reaching diffusive equilibration ($Dt/L^2 = 1$) at different path lengths (L), in which the solid material must travel, based on $D = 10^{-6}$ cm^{2}s^{-1} are:

L = 10 μm	t= 1 sec
L = 100 μm	t= 100 sec
L = 1 mm	t= 2.8 hours
L =1 cm	t= 280 hours

About 50% of the diffusive transfer will occur in about a tenth of the above times. Based upon a static liquid for relatively rapid equilibration by diffusion alone the distance L across the liquid from a solid surface should not be greater than 100 μm. This has an impact on the liquid volume which may be used in static liquid device of the invention, i.e. preferably a liquid volume up to 10nl, preferably up to 5nl.

The consequent limitation on liquid volume can however be readily removed if the liquid is mixed by convective/advective processes within the device and this is a further feature of the invention. Most simply the fluid is stirred *in situ*, e.g. by small magnet stirrer, such as beads, or the fluid may be recirculated over the solid. Alternatively the liquid may be removed to a mixer chamber and then reintroduced to the compound. This may avoid problem with mechanical abrasion on the solid solute surface generating suspended matter, and may be more compatible with *in situ* observation/monitoring of the dissolving solid surface.

Typical amounts of sample which may be used in this device range from 1 ng to 1 mg, the minimum figure corresponds to the region being and indent corresponding to a 10 micron side cube. Typical amounts of liquid used in this device range from 1 nl to 1 ml, the minimum liquid volume corresponds to a 100 μm side cube. A chamber within the device for presenting liquid to the solid sample need not be in the form of a cube but for rapid diffusive transfer no portion of fluid within the chamber should be maintained at a distance from the solid sample much greater than 100μm. It may be useful to present a small solid filled indent

to a very large volume of stirred liquid to determine a maximum dissolution rate in the absence of any tendency to saturate.

It will be appreciated that a true measurement of the solubility of the sample is only possible once sufficient time has elapsed for the sample to be fully dissolved and equilibrium is reached. It will be appreciated that the amount of liquid used will limit the maximal measurement of solubility that may be determined, for example if 0.01mg of solid sample is fully dissolved in 0.01ml of liquid then the maximum determined measurement of solubility of the sample is - at least - mg/ml- the exact measurement could be close to this figure or higher. However, in certain fields it is more useful to determine which samples are poorly soluble in a certain solvent, or that a sample has at least a certain value of solubility in a solvent. Therefore, such limitations are not necessarily critical and the amount of liquid used may be selected such that if all the sample is dissolved in the liquid then the solubility of the samples is acceptable or if any sample remains then the sample is not sufficiently soluble. In such systems it is not necessary that the detector measures the amount of solid sample removed from the region by the liquid. The detector need only determine the presence or absence of compound in the region. Where the amount of solid sample deposited in the region and the amount of liquid is known then the absence of any solid sample at the region after exposure to the liquid indicates a minimum solubility that the sample possesses. The parameters of sample deposited and liquid used may be set such that the minimal solubility measured is at a cut of point to indicate whether the sample passes or fails the test.

It is possible that the rate of dissolution of a sample can be measured in the same system or device as described above by measuring the amount of sample removed from the region by the liquid at various time points before equilibrium is reached.

As a further feature of the invention we disclose a method for determining the rate of dissolution of a sample in a micro-fabricated device the method comprising:

(1) introducing a liquid to a solid sample containing region within the micro-fabricated device;

(2) at time points after introduction of the liquid measuring the amount of solid sample removed from the region;

(3) determining the rate of dissolution by reference to the measurement of solid sample removal from the region and the amount of liquid used over time.

Measurement of rate of dissolution may be carried out where the liquid, preferably of predetermined volume, is presented to the solid sample and remain static while measurements are performed. Alternatively dissolution rates may be carried out by measurement with the liquid volume stirred or recirculated, as described above, or where fresh liquid is fed through the chamber containing the solid sample receiving region.

Additional steps which may be performed in the above methods include extracting the liquid prior to taking the measurement of solid sample removed from the region and/or an initial step of introducing the solid sample into the region of the micro-fabricated device.

It should be understood that the arrangement, type and dimensions of the device and the components therein will vary according to the use or application.

In this disclosure, the term "micro-fabricated" includes devices including structures capable of being fabricated with lengths in one or more dimensions of less than 1 mm, and especially fabricated on or into planar solid substrates such as silicon wafers using methods readily available to those practising the art of silicon micro-fabrication. Such micro-fabricated devices may have features of sizes and geometries producible by such means such as photolithography, isotropic and anisotropic etching by wet or dry methods, thick and thin film deposition methods including printing, screen printing, spin and dip coating, evaporation, sputtering, chemical vapour deposition, LIGA, thermoplastic micro-pattern transfer, resin based micro-casting, micro-moulding in capillaries (MIMIC), laser assisted chemical etching (LACE), and reactive ion etching (RIE), or other techniques known within the art of micro-fabrication. Planar substrates such as silicon wafers may accommodate single devices or a plurality of the devices of this invention in the same or a plurality of configurations. Wafers are available with standard sizes which include wafers with diameters of 3" (7.5cm), 4"(10cm), 6"(15cm), and 8"(20cm), but the structures may be formed on substrates of other dimensions. Application of the principles presented herein using new and emerging micro-fabrication methods is within the scope and intent of the invention.

In this disclosure, the term "liquid" means any liquid for which the solubility of the sample is desired to be determined within, for example aqueous, non-aqueous, protic, aprotic,

buffered or non-buffered, or mixtures of any thereof. The liquid may interact with the solid sample simply to achieve physical dissolution alone or may effect some chemical reaction including ionisation, ligand addition, solvation or hydrolysis. Liquid is introduced to the region such that the liquid and solid sample are brought into contact. Ideally the liquid is delivered as a predetermined volume of liquid. The liquid may be delivered such that it remains static over the solid sample for a period of time prior to or after the measurement is made by the detector. Alternatively the liquid may be streamed across the solid sample containing region and the measurement taken during or after streaming has been completed. In a further alternative the liquid is streamed over the sample several times by continuous recirculation or by an oscillating motion of the liquid. In a further alternative version the liquid is removed from the solid sample, mixed, and then reintroduced to the solid sample. Motion of the liquid may be achieved by the use of physical forces, such as pressure, inertial forces, capillary forces, or the application or variation of electric or magnetic fields. Non liquid fluids such as super critical fluids and gases and vapours may be substituted for liquids in the above description with the process of dissolution into a liquid being equated generally to the transfer of solid as molecular species into the fluid phase. For gases or vapours the process of solid transfer into the gas phase may include evaporation, sublimation, or reaction such as oxidation generating gaseous or volatile products.

As described above the option to recirculate or mix the liquid allows for a larger volume of liquid to be used without unduly extending the time needed to allow diffusional equilibrium. Therefore, in a preferred aspect, liquid of up to 1 ml or above may be used, preferably up to 0.5ml, and ideally up to 100µl.

By high throughput we mean that the invention can achieve a throughput substantially higher than conventional means often 10 to 100 fold increases. In order to achieve the higher throughputs, the method optionally involves parallel processes, i.e. multiple indents are used in parallel. One sample may be tested with several different liquids or several samples may be tested with one or several liquids.

The invention also allows for the simple measurement of the rate of dissolution by placing several identical samples in parallel indents and for each sample exposing it to the liquid for different periods of time. Alternatively the above mentioned process may also simultaneously measure solubility by allowing one or more samples to equilibrate with the

liquid. Alternatively the rate of dissolution is measured by taking measurements of the solid sample remaining in the indent at various time points after application of the liquid, necessitating a detector which can operate with the liquid present on the sample, and optionally a final measurement of solubility once equilibrium has been reached.

In particular we describe as a feature of the invention an on device detection system where the disappearance of the solid is determined using optical techniques, such as interferometry, see Fig 2. The light focused on the sample produces an interference pattern on a suitable focusing device by virtue of the scale and the physical arrangement of features of the grid or mesh and the wavelength of light. As the compound dissolves the intensity of the interference pattern will change. The rate of change will be related to the rate of dissolution of the compound.

The invention is illustrated below by the following non-limiting examples.

Examples

Optical Detector

Using an arrangement as shown in Figure 2 a diffraction pattern is produced, where the horizontal surfaces of the micro-fabricated device are reflective and the compound is less reflective than the surface of the micro-fabricated device. As the compound dissolves lower reflective horizontal surfaces of the micro-fabricated device are exposed. This will not affect the position of the diffraction pattern but will intensify the lower order diffraction bands. Whilst we do not wish to be bound by theory the intensity of the bands is governed by the formula

$$I(\theta) = \frac{I(O)}{N^2} (\mathrm{Sin}\beta/\beta)^2 (\mathrm{SinN}\alpha/\mathrm{Sin}\alpha)^2$$

where I (θ) is the central peak intensity, N is the number of grating lines and where

$$\alpha = \frac{ka}{2} \quad \text{and} \quad \beta = \frac{kb}{2}$$

where k is the order number, a is the pitch of the grating and b is the width of the reflective horizontal surfaces of the micro-fabricated device.

Therefore, as compound dissolves 'a' will remain constant and 'b' will increase. At the point that all compound dissolves the surface will be completely reflective and there will be no diffraction pattern. To avoid complicating interference effects the difference in path length for reflections from each layer of reflective surface will preferably be multiples of the wavelength of light in the medium in which measurements are carried out. Where measurements are carried out without removal of the solvent the medium is the solvent used. For light incident to the surface the height difference between of reflective surface will ¼ of the wavelength of light and cosine θ or multiples thereof.

Alternatively, some wells or areas of the device shown in Figure 2 may alternatively be left unfilled with solid sample and wells in between left empty to be filled with liquid when applied. Then, assuming all the liquid is in equilibrium, which would happen over time, the effect of the refractive index of the solvent could be compensated for.

Figure 3 shows the output expected from a device of figure 2.

Alternative grating based optical methods may be used to measure the dissolution of solid compound from a surface. Using structures of the type represented in Figure 4 allows the periodicity of a grating to be altered as solid compound dissolves. In the example shown in Figure 4 the dissolution of sample within the indent so that the solid sample surface initially at position 1 is changed to position 2 exposing a reflective surface in the centre of a well or trench will double the number of lines per unit length of the grating. This change in grating period enables detection by means of a change in diffraction angles or spectral shift. Similar arrangements where other changes in grating feature spacing are achieved may be achieved by different positioning of reflective surfaces in the wells.

An alternative arrangement indicated in Figure 5 employs the progressive exposure of a group of adjacent steps to generate an expanding grating or reflective surface which can be monitored optically.

Electrochemical Detector

Forming a series of wall structures overlying a conductive electrode structure allows sample to be retained on the electrode surface contained in indents. Exposure of the electrode by dissolution of the sample is monitored by monitoring a cell impedance as indicated in Figure 6

Mass Detector

Alternatively we describe a device where disappearance of the compound is detected by piezo sensors such as quartz crystal devices and which may include Surface Acoustic Wave sensors, which are particularly suited to operation on a miniaturised scale. Such sensors provides an output related to the mass of material adherent to the device surface. A plane mass sensor with sample feature formed on the structure is illustrated in Figure 7.

Fig. 1

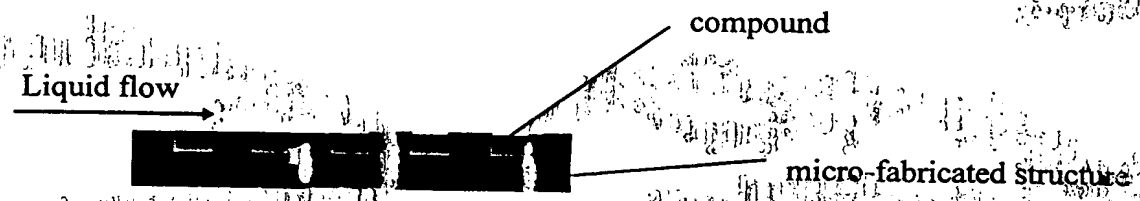
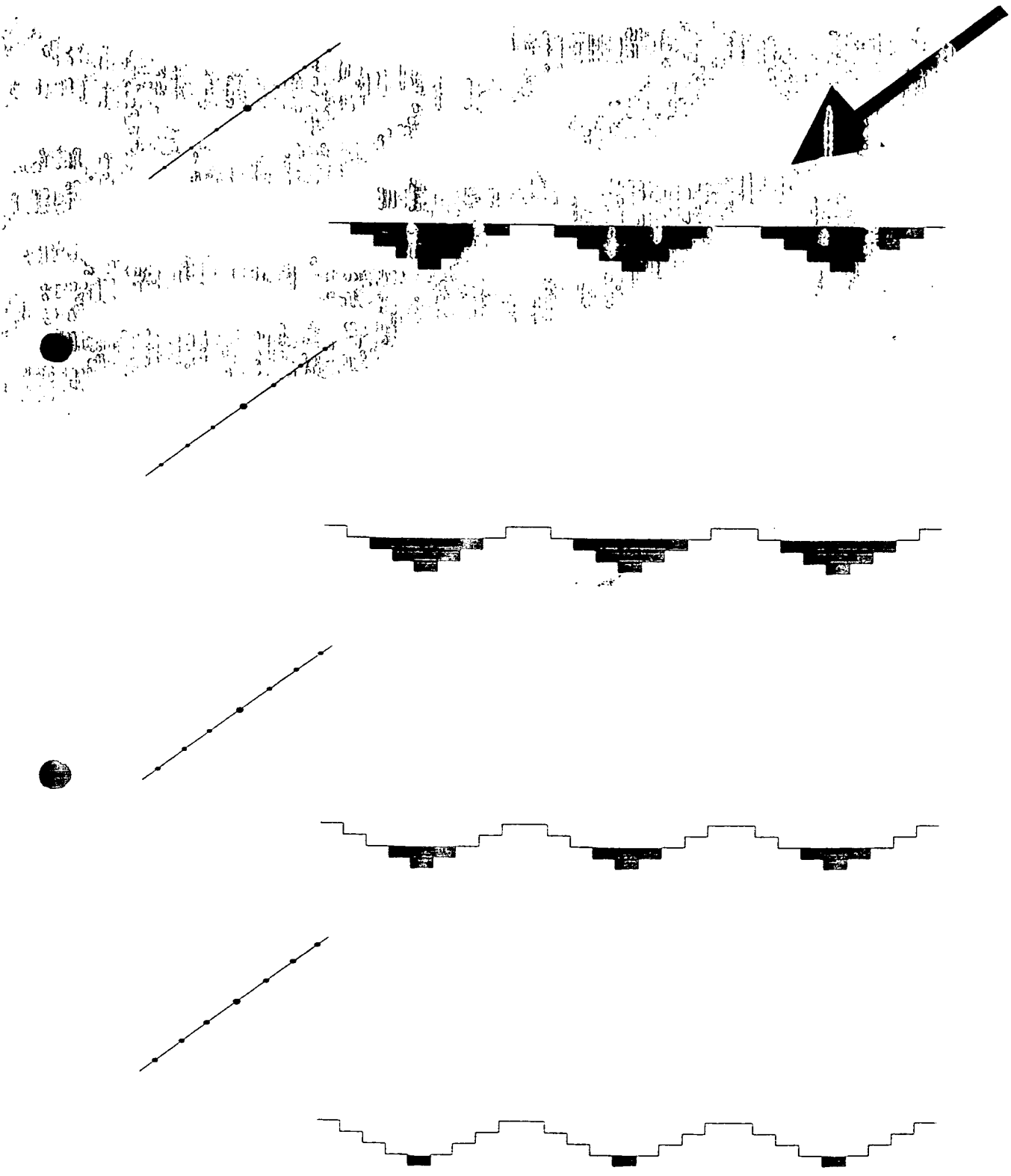


Fig.2



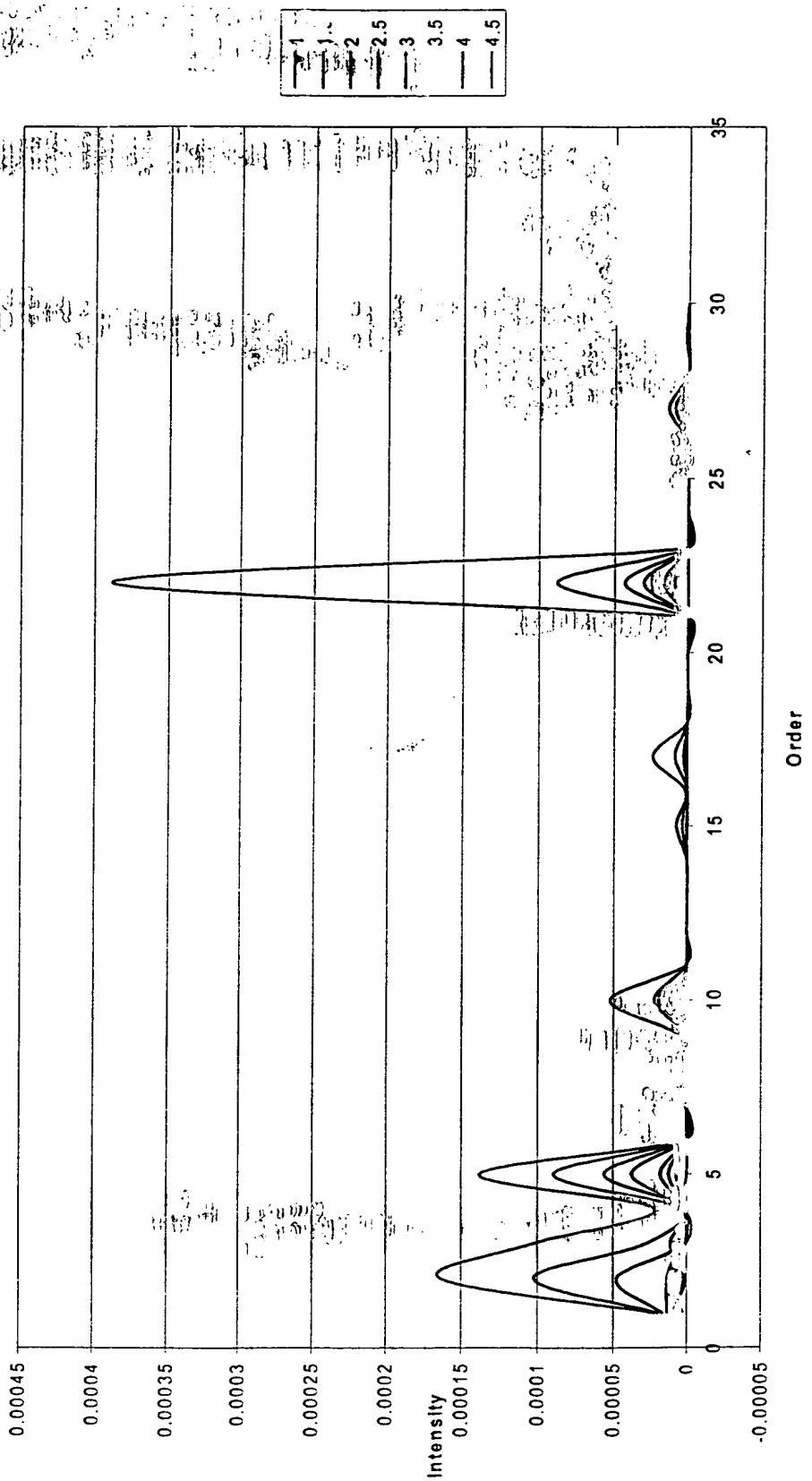

1
1.5
2
2.5
3
3.5
4
4.5
0.00045
0.0004
0.00035
0.0003
0.00025
0.0002
0.00015
0.0001
0.00005
0
-0.00005
Intensity
0
5
10
15
20
25
30
35
Order

Fig.3

Fig.4

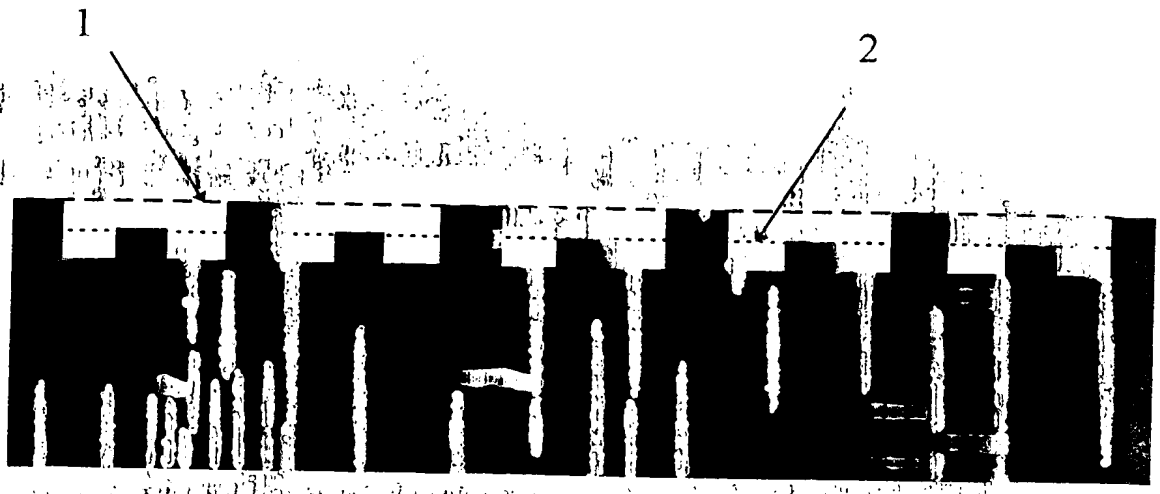


Fig.5

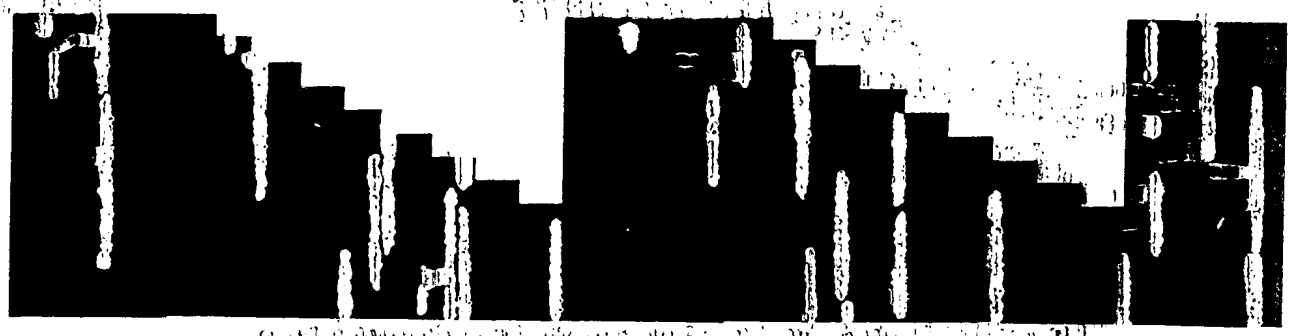


Fig.6

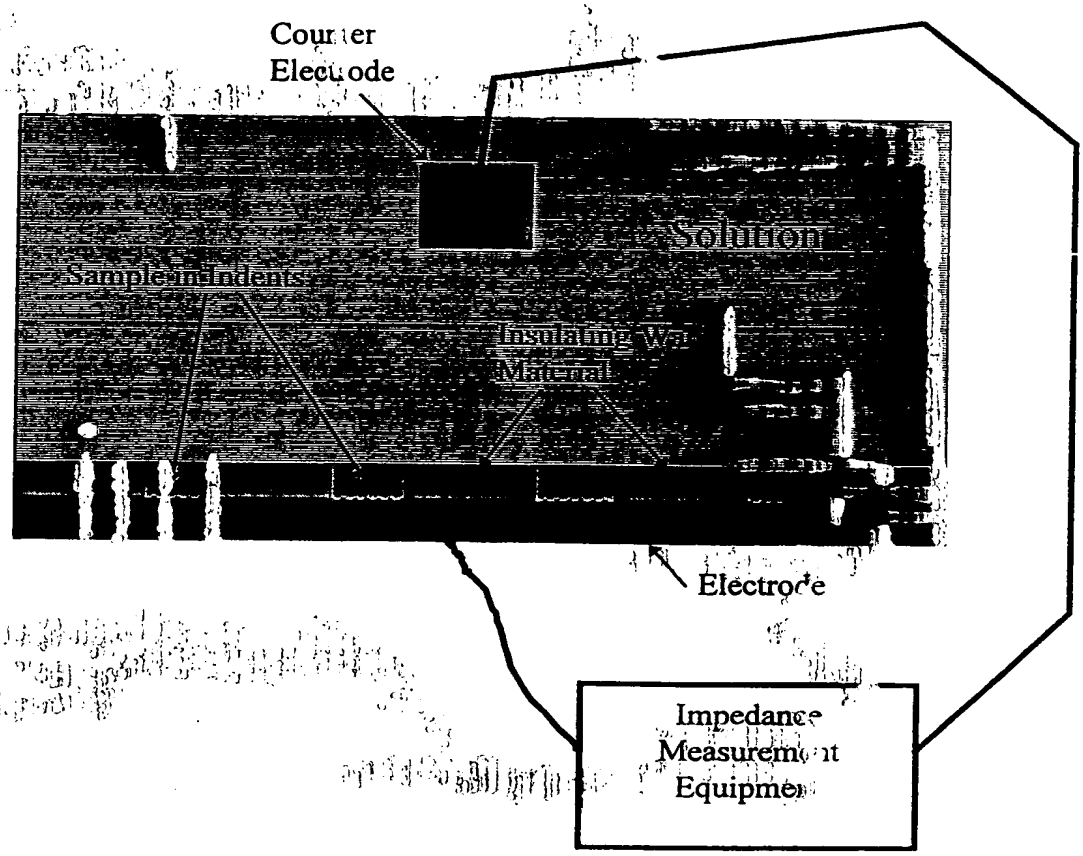
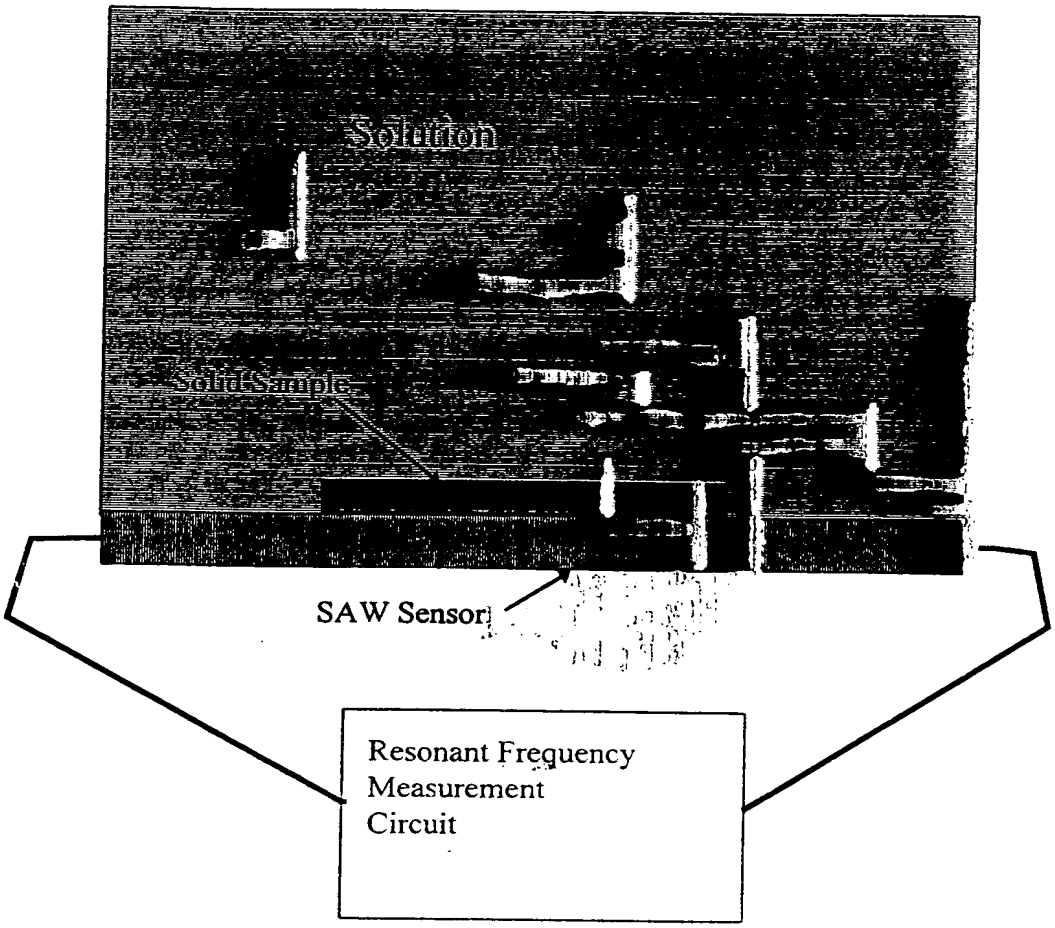

Counter
Electrode
Solution
Sample Analytes
Insulating
Material
Electrode
Impedance
Measurement
Equipment

Fig.7


Solution
Solid Sample
SAW Sensor
Resonant Frequency
Measurement
Circuit